Original Article

The Risk of Clinically Diagnosed Alzheimer Disease in Patients with Non Insulin Dependent Diabetes Mellitus

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ABSTRACT

Background: The role of DM as a risk factor for cognitive decline in later life has received little epidemiological attention until recently. This is despite the high prevalence of diabetes (especially type 2) in older populations. **Objective:** To compare between the risk of development of Alzheimer disease (AD) in patients with and without non-insulin dependent diabetes mellitus (NIDDM). **Methods:** This study is a longitudinal cohort study. For up to 2 years, 764 subjects underwent annual evaluation that included medical history, neurological examination, neuropsychological performance testing, and review of a brain scan when available. For a diagnosis of probable Alzheimer's disease, the criteria adapted from the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA). **Results:** Diabetes mellitus was present in 106 (13.9%) of the participants. During a mean of 2 years of observation, 137 persons developed AD. In a proportional hazards model adjusted for age, sex, and educational level, those with diabetes mellitus had a 61% increase in the risk of developing AD compared with those without diabetes mellitus (hazard ratio, 1.53; 95% confidence interval, 0.96-2.45). The risk of incident dementia was clearly modified by baseline treatment), with the lowest relative risk in newly discovered or untreated diabetic patients (RR 1.3, 95% CI 0.7 to 2.3) and the highest RR among patients treated with insulin (RR 4.3, 95% CI 1.7 to 10.5). **Conclusion:** Patients with NIDDM; particularly those treated with insulin may be at an increased risk of developing AD. **[Egypt J Neurol Psychiat Neurosurg. 2010; 47(3): 419-424]**

Key Words: Alzheimer's disease, NIDDM.

INTRODUCTION

The role of DM as a risk factor for cognitive decline in later life has received little epidemiological attention until recently. This is despite the high prevalence of diabetes (especially type 2) in older populations, the high prevalence of dementia, and several potential mechanisms; by which it may cause cognitive decline[1].

In cross-sectional studies[2-4], diabetes mellitus has been associated with various adverse health effects, including cognitive impairment. The association of diabetes mellitus with impaired cognitive function suggests that diabetes mellitus may contribute to Alzheimer disease (AD).

However, few prospective studies have examined the association between diabetes mellitus and incident AD, and their results have been inconsistent, with some studies[5,6] finding that persons with diabetes mellitus are at increased risk for AD and others[7,8] not finding this association.

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Many factors may mediate an association between diabetes and AD. A post-mortem study of brains of diabetic patients found no evidence of increased Alzheimer's pathology compared to age-matched controls [9] suggesting more a role of exacerbating pre-existing disease[1].

The aim of this study was to compare the risk of developing AD in subjects with and without DM.

SUBJECTS AND METHODS

A number of 876 patients referred to the Department of Neuropsychiatry, El-Menoufia University and Tanta University Hospitals were enrolled in this study starting from January 2006 to January 2008. The mean age was 68±4 years. Sixty-tow (7.0%) had dementia at baseline and were excluded from all analyses.

Of the 814 participants without dementia, 19 died before the first follow-up evaluation and 31 enrolled in the previous year and had not yet reached the scheduled date of their first follow-up evaluation.

This left 764 persons eligible for follow-up. Analyses were based on this group of patients, who underwent annual clinical evaluations.

Missing data have reflected relocation, withdrawal from all or part of the study, and incapacity or unwillingness to complete selected evaluation procedures.

All patients gave their informed consent and they underwent extensive clinical, radiological, and neuropsychological evaluation.

Exclusion Criteria:

1- Patients having mixed vascular and Alzheimer dementia. Vascular dementia was diagnosed by sudden or stroke-related onset, presence of lateralizing neurological signs, and MRI brain.
2- Patients having other types of dementia.
3- Patients having dementia at the baseline of the study.
4- Patients who develop diabetes mellitus after the onset of AD during the period of follow up.
5- Patients having type-I DM.
6- Presence of pseudo-dementia (depressive disorder).

At baseline, each subject underwent a uniform structured clinical evaluation that followed the procedures recommended by the Consortium to Establish a Registry for Alzheimer's disease. The evaluation included medical history, neurological examination, neuropsychological performance testing in the form of MMSE test, and review of a brain scan when available. The CT brain was restricted to those having straight forward radiological diagnosis and did not need more verification by MRI brain.

For a diagnosis of probable Alzheimer's, the criteria adapted from the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) include:

- Dementia established by examination and objective testing
- Deficits in two or more cognitive areas
- Progressive worsening of memory and other cognitive functions
- No disturbance in consciousness
- Onset between ages 40 and 90.

Diabetes mellitus was considered present if the participant was taking a medication to treat diabetes mellitus, reported a history of diagnosis of diabetes mellitus, or both.

Follow-up evaluations were identical in all essential details to the baseline evaluation, and were performed annually by examiners blinded to previously collected data.

Statistical Methods

All analyses adjusted for age, sex, and educational level. Cox proportional hazards models were used to estimate the risk of AD among persons with diabetes mellitus compared with those without diabetes mellitus.

Random effects models were used to test the effects of diabetes mellitus on baseline level of function and annual rate of change (fixed effects) while adjusting for person-specific paths of cognitive change with random effects.

RESULTS

Diabetes mellitus was present in 106 (13.9%) out of the 764 participants included in these analyses at baseline. Out of the 106 participants with diabetes mellitus, 96 (90.57%) were taking medication for the treatment of diabetes mellitus: 46 were taking insulin only, 40 were taking an oral hypoglycemic only, 10 were taking both and 10 patients were under no treatment at all. Overall, there were more men in the group with diabetes mellitus (Mentioned table).

During the follow-up evaluations, 137 persons developed AD, of whom 25 had diabetes mellitus. (In a proportional hazards model adjusted for age, sex, and educational level), there was a 61% increase in the risk of developing AD in those with diabetes mellitus compared with those without diabetes mellitus (hazard ratio, 1.53; 95% confidence interval, 0.96-2.45) The cumulative hazard of AD over time, adjusted for age, sex, and educational level, is shown graphically in Figure 1 for typical participants with and without diabetes mellitus.

The risk of incident dementia was clearly modified by baseline treatment, with the lowest relative risk in newly discovered or untreated diabetic patients (PR 1.3, 95 % CI 0.7 to 2.3) and the highest RR among patients treated with insulin (RR 4.3, 95% CI 1.7 to 10.5).

Table 1. General Characters of the sample.

Characteristic	Subjects with diabetes mellitus N = 106	Subjects without diabetes mellitus N = 658
Age at base line	68.3 (4.5)	69.2 (5.3)
Male sex, No. (%)	46 (43.4)	269 (40.88)
Education, Y	14.3 (3.5)	14.4 (3.6)
MMSE Score at base line	26.2 (1.5	26.4 (1.5)

Data are expressed as mean (SD) unless otherwise indicated
MMSE Mini-Mental State Examination.

Table 2. MMSE Scores of the Alzheimer's disease patients with and without Diabetes mellitus.

MMSE Scores	Subjects with DM No=106	Subjects without DM No=658
≤ 10	1	2
11-15	19	43
16-19	22	57
20-22	15	10
23-24	14	93
25	12	154
27-28	16	177
29-30	7	142
Total	106	658

DM Diabetes mellitus, ***MMSE*** Mini-Mental State Examination.

Table 3. Types of treatment of diabetes mellitus in diabetic Alzheimer's disease patients.

Type of Treatment	Number	Percentage (%)
Under insulin	46	43.41
Under oral treatment	40	37.73
Under both	10	9.43
Not under treatment	10	9.43
Total	106	100

Table 4. MMSE Orientation scores of Alzheimer's disease patients with and without Diabetes mellitus.

Scores of Orientation	Diabetic		Non Diabetic	
	Number	Percentage (%)	Number	Percentage (%)
0 – 3	13	52	47	41.96
4 – 6	8	32	38	33.93
7 – 10	4	16	27	24.11
Total	25	100	112	100

No statistically significant difference was found between diabetic and non diabetic patients as regard orientation ($p>0.05$).
MMSE Mini-Mental State Examination.

Table 5. MMSE scores of attention & calculation of Alzheimer's disease patients with and without Diabetes mellitus.

Scores of Attention & Calculation	Diabetic		Non Diabetic	
	No	%	No	%
0 – 2	16	64	53	47.32
3 – 4	7	28	42	37.50
5	2	8	17	15.18
Total	25	100	112	100

A statistically significant difference was found between diabetic and non-diabetic patients as regard attention and calculation ($p<0.05$).
MMSE Mini-Mental State Examination.

Table 6. MMSE scores of recall of the Alzheimer's disease patients with and without Diabetes mellitus.

Scores of Recall	Diabetic		Non Diabetic	
	No	%	No	%
0	17	68	25	22.32
1	4	16	45	40.18
2	2	8	30	26.78
3	2	8	12	10.72
Total	25	100	112	100

A statistically significant difference was found between diabetic and non diabetic patients as regard recall ($p<0.001$).
MMSE Mini-Mental State Examination.

DISCUSSION

In this study on more than 800 older persons, we found that diabetes mellitus was associated with an increased risk of developing AD during 2 years of observation. The risk of incident AD was 61% higher in those with diabetes mellitus than in those without it. These results suggest that diabetes mellitus may be related to risk of AD in old age.

These findings are consistent with the results of 3 large longitudinal cohort studies.[5,6] Ott et al.[5], found that diabetes mellitus doubled the risk of AD during 2 years of follow-up in a sample of more than 6000 older persons from a defined cohort. Peil et al.[6], using data from about 2500 Japanese American men, found a similar result: diabetes mellitus approximately doubled the risk of AD. Xu et al., found that the risk of incident AD was 65% higher in those with diabetes mellitus than in those without it. It is found recently that even borderline diabetes is associated with increased risks of dementia and Alzheimer's disease; the risk effect is independent of the future development of diabetes[10].

In contrast, 2 other longitudinal studies[7,8] did not demonstrate a significant association between diabetes mellitus and incident AD, but in both, the results were in the direction of increased risk. Also, in the Framingham cohort, overall Diabetes mellitus did not increase the risk of incident AD; however, DM may be a risk factor for AD in the absence of other known major AD risk factors[11].

Some case-control studies have reported a negative association between type 2 DM and AD[12-14] that suggested a possible protective effect of high glucose on the brain, but these studies have been of small size or have used referred patients with AD open to selection bias[15].

The basis of the association between diabetes mellitus and AD is uncertain. The burden of Alzheimer's pathology may be increased by systemic vascular disease. The distribution of amyloid in white matter was found to be related to blood vessels, suggesting a vascular rather than a neuronal source[16]. Increased permeability of the blood-brain barrier occurs secondary to transient ischaemia[17], and this process may underlie both perivascular amyloid deposition and white matter lesions[18].

However, the increased risk of AD associated with type 2 DM may be mediated to a large extent by non-vascular mechanisms[19]. These may include hyperglycemia compounding the ischemic burden of pre-existing vascular disease by increasing anaerobic metabolism and lactic acidosis[20].

In addition, the disturbances of neurotransmitters may be involved as decreased cholinergic transport across the blood-brain barrier which may be potentially important in exacerbating cognitive impairment in the presence of subclinical AD[21]. Butyrylcholinesterase and acetylcholine-esterase related proteins were found common to both Alzheimer's disease and diabetes; they may play an etiological role via influencing insulin resistance and lipid metabolism[22]. Also, diabetes may have a role in dysfunctional glutamate receptors leading to an impaired hippocampal synaptic plasticity[23].

Our results showed that the lowest relative risk of developing AD was in newly discovered or untreated diabetic patients and the highest RR among patients treated with insulin. This is in agreeing with the study that showed particular strong associations between dementia and diabetes treated with insulin. The relation was strongest with vascular dementia, but was also observed with AD[24].

Many important components of Alzheimer's disease appear to stem from imbalances in insulin signaling intrinsic to the brain, rather than systemic insulin imbalances, and that treatments aimed at redressing insulin imbalances in the brain could be effective therapies[25].

Insulin has been shown to inhibit synaptic activity at excessively high or low levels[26], and down regulate choline acetyltransferase[27]. Moreover, a role for insulin and insulin growth factor-1 (IGF-1) in the regulation of tau protein phosphorylation has been suggested[28], the process underlying the formation of neurofibrillary tangles. IGF-1 prevents amyloid-related neurotoxicity in rats[29]. Deposition of amyloid deposit in pancreatic islet beta cells appears to be a consistent pathologic marker in type 2 DM. An islet peptide known as amylin has been identified as the key component of such amyloid deposit[32]. Janson et al. have recently reported an increased frequency of islet amyloid deposition in the pancreas of patients with AD compared with control subjects without AD[31]. Amylin antagonized insulin-induced glycogen synthesis in diabetes[32]. Polymorphic variations in genes involved in mediation of insulin metabolic effects and correlated with increased insulin resistance appear to contribute to the risk of AD, supporting the hypothesis that both diseases may share a common genetic background[33]. Chronic hyperglycemia and advanced age may be associated with increased cerebral sensitivity to hypoglycemic episodes[34,35].

This study has some strengths including the availability of a period of 5 years of follow-up data with annual structured evaluations. Also, this longitudinal study benefits from a high follow-up rate, which minimizes selective attrition effects. Also, the homogeneity of the population may be considered strength of the study, by controlling for

the effects of potentially confounding variables, such as educational level, occupation, and lifestyle.

This study also has several limitations. The identification of persons with diabetes mellitus. Diabetes mellitus was identified using medication data and/or self-report, but not serological data. However, analyses of data on inspection of all medications and on self-report suggested that self-report was a reliable means of assessing diabetes mellitus.

In summary, these findings suggest that diabetes mellitus is associated with increased risk to AD.

[Disclosure: Authors report no conflict of interest]

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الملخص العربى

دراسة مخاطر حدوث مرض الزهايمر إكلينيكياً في مرضي البول السكري

الهدف من البحث : المقارنة بين مخاطر حدوث الزهايمر في مرضي البول السكري.

طريقة البحث : أجريت هذه الدراسة خلال سنتين فى الفترة من 2006 إلي 2008 على 764 شخص وأجريت لهم تقييم شمل التاريخ المرضي، اختبار الجهاز العصبي والاختبارات النفسية العصبية في صورة مقياس MMSE مع عمل أشعة مقطعية على المخ لبعض المرضي.

النتائج : كان مرض البول السكري يوجد عند 106 مريض من المشاركين في البحث وفى خلال عامين من الملاحظة والمتابعة للمرضي وجد أن 137 أظهروا إكلينيكياً أعراض مرض الزهايمر منهم 25 ممن أصيبوا بمرض البول السكري و112 مريض لم يعانوا من مرض البول السكري.

وقد وجد من النتائج أن هؤلاء الأشخاص الذين يعانون من مرض البول السكري يزيدون بنسبة 61 % في خطورة تعرضهم لمرض الزهايمر بالمقارنة مع هؤلاء الذين لا يعانون من مرض البول السكري وكذلك وجد أن نسبة مرض الزهايمر تقل في هؤلاء المرضي بالبول السكري في مرحلة بداية المرض والذين لم يبدأو العلاج بعد وتزداد النسبة أكثر في هؤلاء المرضي بالبول السكري كلما زادت مدة المرض والعلاج بالأنسولين.

الخلاصة : أن المرضي الذين يعانون من مرض البول السكري (NIDDM) وخاصة الذين يعالجون بالأنسولين يكونوا عرضة أكثر من غيرهم بالإصابة بمرض الزهايمر.